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***De novo* variants in *CDK13* associated with syndromic ID/DD;  
molecular and clinical delineation of 15 individuals and a further  
review**

Running title: *De novo CDK13* variants associated with ID/DD

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**Conflict of interest** All contributors have read and approved the submission to the journal. M. Cho, A. Begtrup, and R. Willaert are employees of GeneDx. We are not aware of any other conflict of interest.

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**Abstract**

*De novo* variants in the gene encoding cyclin-dependent kinase 13 (CDK13) have been associated with congenital heart defects and intellectual disability (ID). Here, we present the clinical assessment of fifteen individuals and report novel *de novo* missense variants within the kinase domain of CDK13. Furthermore, we describe two nonsense variants and a recurrent frame-shift variant. We demonstrate the synthesis of two aberrant *CDK13* transcripts in lymphoblastoid cells from an individual with a splice-site variant. Clinical characteristics of the individuals include mild to severe ID, developmental delay, behavioural problems, (neonatal) hypotonia and a variety of facial dysmorphism. Congenital heart defects were present in two individuals of the current cohort, but in at least 42% of all known individuals. An overview of all published cases is provided and does not demonstrate an obvious genotype-phenotype correlation, although two individuals harbouring a stop codons at the end of the kinase domain might have a milder phenotype. Overall there seems not to be a clinically recognizable facial appearance. The variability in the phenotypes impedes an à vue diagnosis of this syndrome and therefore genome-wide or gene-panel driven genetic testing is needed. Based on this overview we provide suggestions for clinical work-up and management of this recently described ID syndrome.

**Keywords:** *CDK13*, Congenital Heart Defects, *de novo* variants, Developmental Delay, Facial Dysmorphism, Intellectual Disability, Splice-site variant, Whole-Exome Sequencing

CDK13 (cyclin-dependent kinase 13, OMIM 603309) is a ubiquitously expressed serine/threonine kinase. This kinase uses ATP as source of phosphate groups and forms, in conjunction with cyclin K, a protein complex which positively regulates transcription through phosphorylation of RNA polymerase II (1). Furthermore, CDK13 is involved in alternative splicing of RNA (2, 3) and its mouse homologue regulates axonal elongation (4).

Recently, *de novo* missense variants located in the kinase domain of *CDK13* have been reported (5-8). Sifrim and colleagues describe seven individuals with congenital heart defects, mainly of the ventral and atrial septa (6). In addition, these individuals showed developmental and motor delay, intellectual disability (ID) and various facial dysmorphisms among other features. A further six female individuals with *de novo CDK13* variants were reported from the Deciphering Developmental Disorders project (7). Common phenotypic characteristics of these individuals included ID and dysmorphic facial characteristics. Bostwick *et al.* (5) describe another nine individuals, showing a similar phenotype with developmental delay(DD)/ID, congenital heart defects, hypotonia and facial dysmorphisms. It is of note that all reported variants in that study are *de novo* missense variants, with one recurrent variant (p.Asn842Ser) reported in seven non-related individuals. Hamilton and colleagues (8) provide extensive clinical information on 16 cases, which included an update on 13 previously reported individuals (5, 7).

In the present study, we performed a clinical evaluation of fifteen previously unreported individuals with *de novo CDK13* variants. Importantly, in addition to novel missense variants, we describe for the first time nonsense variants in *CDK13*. This extended cohort, combined with the 25 previously reported individuals, enables us to provide an improved description of the syndromic phenotypic spectrum of individuals with *de novo* variants in *CDK13*.

## Individuals and methods

### *Recruitment and examination of individuals with CDK13 variants*

Clinical child-parents whole-exome sequencing (trio-WES) at the Department of Human Genetics at the Radboudumc (Nijmegen, The Netherlands) (9, 10) resulted in the identification of four individuals with *de novo* variants in *CDK13*. One individual is a monozygotic twin and the same variant was detected in her sister by re-sequencing. Another individual was identified by single-case WES. Ten additional individuals with *de novo* variants in *CDK13* were recruited based on a 'genotype-first approach' via GeneMatcher (11) and had undergone clinical exome sequencing in different genetic laboratories in The Netherlands and the United States of America. The reference sequence used for *CDK13* is RefSeq NM\_003718.4. All here reported and previously reported variants (Suppl Table 3) are absent from the ExAc database (12) as well as the extended version of this database (gnomAD, <http://gnomad.broadinstitute.org/>). All individuals were examined by a clinical geneticist and their natural history was reviewed. This study was approved by the institutional review board of the Radboud University Medical Center (Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen NL36191.091.11). Informed consent was obtained for publication of the shown clinical photographs.

### *mRNA analysis*

To study the effects of a splice-site variant in intron 7 of *CDK13* in mRNA from Individual 10, lymphoblastoid cell lines were generated from peripheral blood cells by Epstein-Barr virus transformation following standard procedures (13). To check for the occurrence of nonsense-mediated decay, mRNA was isolated from cells that were cultured in the presence/absence of cyclohexamide. *CDK13* mRNA was analyzed by the synthesis of cDNA and Sanger sequencing according to standard protocols.

## Results

### Genetic characterisation

We identified a broad range of *CDK13* variants among the fifteen individuals (Table 1). In addition to missense variants, nonsense variants and a splice-acceptor variant were present among this cohort. The variants were shown to have occurred *de novo* in all but one individual; the parents of Individual 13 were not available for testing. The four different missense variants, of which three are novel, all lead to changes in the protein kinase domain of CDK13 (aa 697-1029), of which two are in (p.Gly714Asp) or close to (p.Arg737Cys) the ATP-binding region (aa 711-734) (Fig.1A). The p.Asn842Ser substitution within the kinase-active site (aa 833-845) (6), was observed in five of the fifteen individuals. Taken together, all missense variants affect evolutionary highly conserved regions of CDK13 and were anticipated to be deleterious by different prediction algorithms (Supp. Table 2). The two nonsense variants (c.2995C>T, p.Arg999\* and c.3073C>T, p.Arg1025\*) are expected to result in a dysfunctional CDK13 by missing one third of the protein. Alternatively, nonsense-mediated decay of the transcripts might occur leading to a clear reduction in protein level. The frame-shift variant c.484dup leading to p.Ala162fs was observed in three independent individuals. The consequence of this variant on protein synthesis is not known and might involve a lower protein production in the cell because of nonsense-mediated decay of this transcript but it is also possible that an alternative translational start site is used. The splice-acceptor variant c.2601-2A>G detected in the monozygotic twin pair (Individuals 9 and 10) was predicted to interfere with the correct splicing of intron 7. To test this, we analysed the mRNA region downstream of exon 6 from immortalised lymphoblastoid cells derived from Individual 9. Three different transcripts were detected (Fig.1B). The correctly spliced mRNA was present, supposedly derived from the wild-type *CDK13* allele. Another transcript used a cryptic splice site in exon 8 leading to an out-of-frame coding sequence. In the third splice variant, exons 8 and 9 were missing while the reading frame was conserved in exon 10. The mutant transcripts were apparently not affected by nonsense-mediated decay. It is of note

that all *CDK13* variants seem to affect the protein kinase domain and this likely disturbs the phosphorylation activity of CDK13. None of the reported *CDK13* variants were present in the ExAC/gnomAD databases.

## Phenotypic characterisation

The majority of the individuals (9 female, 6 male) were examined at a young age (<14 y), whereas Individuals 5 and 13 were examined at the age of 22 and 54, respectively (Table 1). Extensive clinical descriptions are given in Supp. Table 1. All individuals displayed DD and/or ID (15/15). The degree of ID was variable and varied mostly from mild to moderate, although Individual 5 had severe ID. Individual 14 displayed DD and behavioural problems but IQ measurement showed a score of 85. Behavioural problems were frequent and diverse, and included autism spectrum disorders (5/15), ADHD (4/15) and hyperactivity (2/15). Not all individuals underwent cerebral imaging but Individuals 3, 5, 8 were shown to have cerebral anomalies on MRI, consisting of focal atrophy of part of the putamen (Individual 5), periventricular leukodystrophy (Individual 8) and Chiari malformation (Individual 3). Speech problems were commonly reported (7/8) and two individuals had not developed speech at their last medical examination at the ages of 8 and 11 years. Feeding problems were frequently reported (10/15), mostly as neonate. Notably, in four cases (Individuals 2, 7, 11, 13) hyperphagia was reported. Individual 11 had, in addition to the *CDK13* variant, a paternally inherited frame-shift variant of *MC4R*, encoding for the melanocortin 4 receptor, and variants of this gene are associated with hyperphagia and obesity (14), thereby explaining her hyperphagia and overweight. Hypotonia was reported in ten individuals. Variable dysmorphic facial features were seen in most individuals (Fig.2) and included philtrum abnormalities, blepharophimosis and strabismus. Macrocephaly (>2.5 SD) was present in three cases, whereas two individuals showed microcephaly (-2.5 SD) and relative short stature (-1.75 SD). The general appearance of some individuals was characterized by a hypotonic posture with sloping shoulders (6/14) and flat feet were common (9/13). Furthermore, gynaecomastia was seen in three of the six male individuals. It

is unknown whether the breast tissue was glandular of origin or a benign fat deposit. Echocardiography was performed in 9 out of 13 individuals. Two individuals had congenital heart defects; Individual 6 had an atrial septum defect and Individual 9 had a patent ductus arteriosus. Cardiac screening of Individual 5 showed borderline dilation of the right ventricle at the age of 24 y.

## Discussion

We evaluated the molecular characteristics and clinical phenotypes of fifteen previously unreported individuals with variants in *CDK13*, of which fourteen were proven *de novo*, and for one individual the parents were not available for testing. A common characteristic and interesting observation of the missense variants is that they all cluster in the kinase domain of the CDK13 protein, and more specifically, variants cluster mostly in and close to the ATP binding site and the active site of the kinase domain. The truncating and splice-site variants also affect this kinase domain. The individuals shared several phenotypic characteristics including ID/DD with behavioural problems and various facial dysmorphisms.

### Spectrum of reported variants

In previous publications on individuals with *CDK13* variants, only missense (n=24) variants and one splice-site variant were reported (5-8) (Suppl. Table 3). Notably, here we describe in addition nonsense and frame-shift variants in *CDK13*. We could not detect a clear genotype-phenotype correlation although individuals 14 and 15 harboring a stop codon at the end of the kinase domain, might show a milder phenotype. Among our group of fifteen individuals, the recurrent missense variant leading to p.Asn842Ser substitution was found in five cases. Over all the variants that have been reported so far, this is the most frequently encountered variant in individuals with the CDK13 syndrome (17/40, 43%). Interestingly, both Bostwick *et al.* (5) and Hamilton *et al.* (8) report another variant at this amino acid position (c.2525A>G,



p.Asn842Asp) which introduces a negative charge in the active site of the protein kinase domain. The variants leading to p.Arg737Cys and p.Arg880Cys were not reported before and locate in the kinase domain as all other reported missense variants do. The marked reduction in the genetic variation in the kinase domain of CDK13 in comparison with other regions of the protein among healthy individuals (12), indeed suggests that little variation is tolerated within the kinase domain. Furthermore, Hamilton et al. (8) performed *in silico* protein modelling to investigate the effect of the variants on CDK13 structure and to gain insight into the possible molecular basis of pathogenicity. The authors presume a dominant negative mechanism, although this is not substantiated by functional studies. In this study, we report three unrelated individuals with an identical frame-shift variant (c.484dup, p.Ala162fs) and we describe two individuals with non-sense variants located at the C-terminal end of the kinase domain. Importantly, these individuals with the frame-shift and nonsense variants were clinically indistinguishable from those carrying missense variants in the kinase region of CDK13 (Supp. Table 1 and Fig. 2).

### Mechanistic models

This observation might suggest that there is a similar mode of action between the two groups of genetic variants, and a haploinsufficiency model might explain that we could not observe a genotype-phenotype correlation. However, currently it is still feasible that (some of) the missense mutations located in the *CDK13* kinase domain have a dominant negative effect. Functional experiments might provide deeper insight into the precise molecular mechanisms of the various *de novo* variants in *CKD13*. The here reported frame-shift and non-sense variants are as well expected to result in haploinsufficiency of the *CDK13* gene. In addition, copy-number losses including the entire *CDK13* gene are strikingly absent from the Database of Genomic Variants (15), which supports a haploinsufficiency mode of action. It is noted that the gnomAD database (November, 2017) contains nine high-confidence non-sense variants and two frame-shift variants (of which one is present twice). The gnomAD database does not include individuals with severe paediatric disease, but mild phenotypes

might be included. It would be of interest to explore the medical history of the concerned individuals. Therefore, based on our current data, we hypothesize that the missense variants in the kinase domain of *CDK13* lead to a structural and/or functional deformation of the kinase domain of CDK13 and abrogate its catalytic function.

### Clinical spectrum and suggestions for clinical practise

In Table 1, we present an overview of the main clinical features of the individuals described in this study and those reported previously (5-8). In total 27 female and 13 male individuals are reviewed. As previously mentioned, there is no obvious correlation between specific gene variants and a specific clinical phenotype. Our study does therefore not support a clear genotype-phenotype correlation. ID/DD is present in all individuals and is mostly accompanied by a variety of behavioural problems, although not all studies report on behavioural aspects. The frequency of structural brain anomalies varied between the different reports. Cerebral imaging was not performed in all individuals. Hypotonia is observed in more than 75% of the individuals, mostly at the neonatal stage. Post-neonatal hypotonia is possibly reflected by the high incidence of pes planus (9/13) and sloping shoulders (in present study, 43%). A variety of facial dysmorphisms are frequently seen in the individuals, with thin lips, eye lid abnormalities and a broad nose/nasal bridge as the most frequently reported features. Stratification of the individuals according to their genetic variants did not reveal consistency of the facial appearance per variant (Table 2). Sifrim and colleagues selected for individuals with congenital heart defects (1,891 individuals) and identified among their cohort seven individuals with *de novo* variants in *CDK13* (6). All these individuals had septal defects. In the other studies, congenital heart defects were observed as well (over all studies 16/38 (42%), Table 2). We suggest echocardiography for individuals with newly discovered *CDK13* variants in the clinical work-up. Because most of the investigated individuals are young children (below the age of fourteen), we recommend to closely monitor the currently identified group of individuals to improve description of the natural course of this syndrome. The identification of individuals with this *CDK13* syndrome

has meanwhile resulted in the formation of parent groups on social media, an important social aspect of current research. We conclude that individuals with *de novo* *CDK13* variants do show a syndromic intellectual disability phenotype, with facial dysmorphisms, congenital heart defects, hypotonia and behavioural problems as the most frequent features. Previous studies (5, 8) reported a recognisable facial gestalt among their individuals with *CDK13* variants. Our study confirms the presence of dysmorphic facial features in all individuals, although the facial phenotype might not be specific nor consistent enough to enable à vue clinical diagnosis. Also, with the increasing number of individuals described, the clinical variation seems to divert further. To further delineate the clinical spectrum associated with *de novo* variants of *CDK13* we established a website to collect detailed clinical information of additional individuals that will be identified over the coming years ([www.humandiseasesgenes.com](http://www.humandiseasesgenes.com)). Based on the current clinical findings of all reported cases, we provide the following suggestions for clinical work-up and management. Early assessment should include, cardiac and neurologic evaluation with special attention for increased seizure risk. The high incidence of hypotonia and neonatal feeding problems requires special attention, close monitoring enabling early intervention to support feeding if needed. Language delay requires proactive speech therapy. As clinical recognition of the *CDK13* syndrome will be challenging, a genotype-first approach, by either WES or ID gene panel analysis (including *CDK13*), will be crucial in diagnosing this new syndrome.

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## Figure legends

*Fig. 1.* Localisation of the amino-acid (aa) residue substitutions in the CDK13 protein of all presently reported and published individuals (5-8), and transcript analysis of a splice-site mutation in *CDK13*. (a) Schematic localisation of all presently and earlier reported *de novo* CDK13 variants. The variants reported in this study are shown above the protein in red and those reported in earlier studies are depicted below the protein in blue. Numbering of aa is based on the wild-type transcript NM\_003718.4. The indicated functional domains of the protein are derived from Kohoutek and Blazek, 2012 (16). (b) Overview of the various transcripts detected in lymphoblastoid cells derived from Individual 9 with the c.2601-2A>G splice-acceptor variant. The wild-type transcript is presumably from the unaffected allele, whereas two other transcripts are a consequence of the splice-acceptor variant. In the first transcript, a cryptic splice-acceptor site is used at position c.2620, whereas in the second one, exons 8 and 9 are skipped and in exon 10 the wild-type open-reading frame is used, which leads to the deletion of 60 aa's in the kinase domain of the encoded protein.

*Fig. 2.* Facial features of individuals with *de novo* variants in *CDK13* presented in this study.

## Supporting information

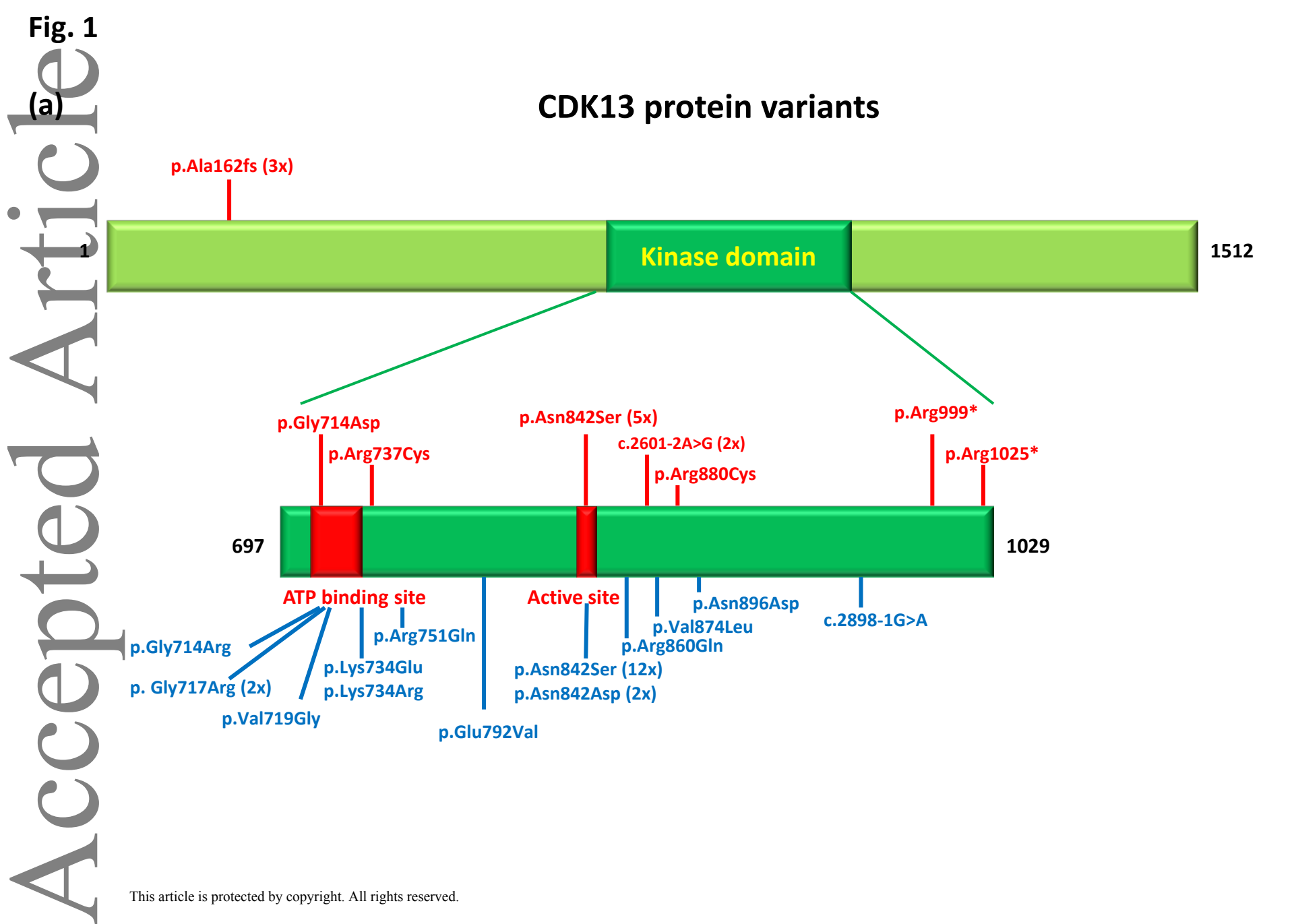
Supplementary Table 1. Clinical features of individuals with variants in *CDK13*.

Supplementary Table 2. Location and conservation of missense variants in *CDK13*.

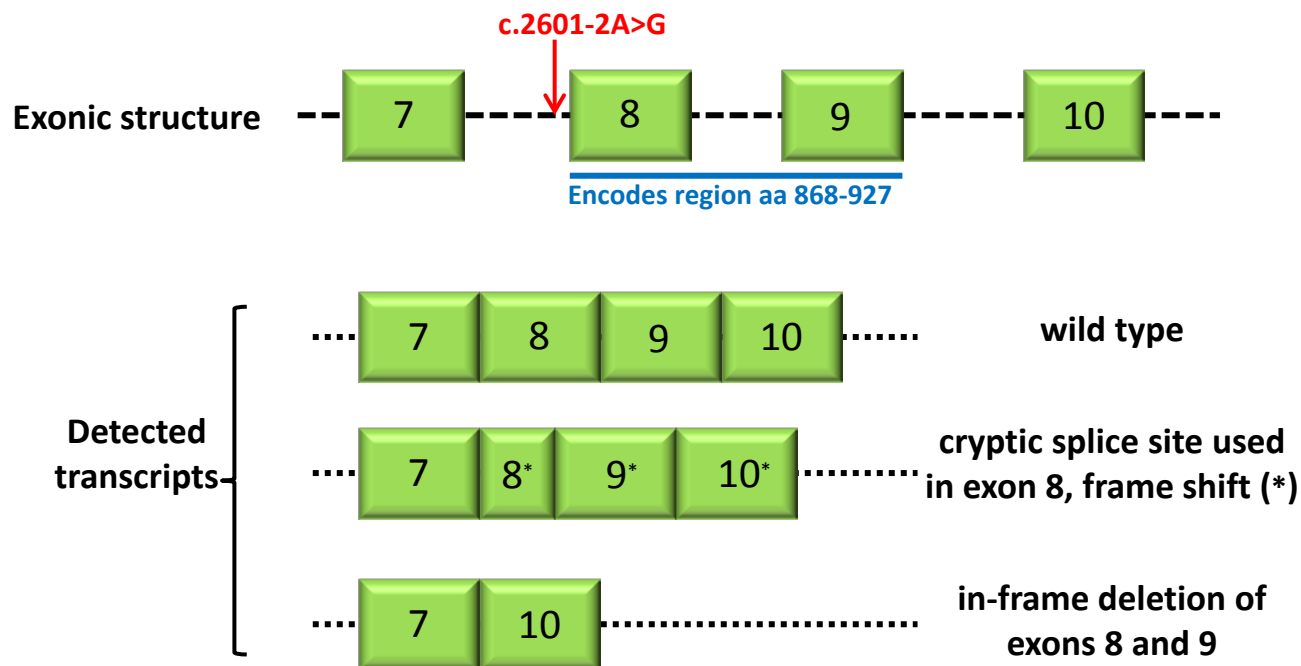
Supplementary Table 3. Reported *CDK13* variants associated with Developmental Delay and/or Intellectual Disability.

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(b)

*CDK13* transcript analysis



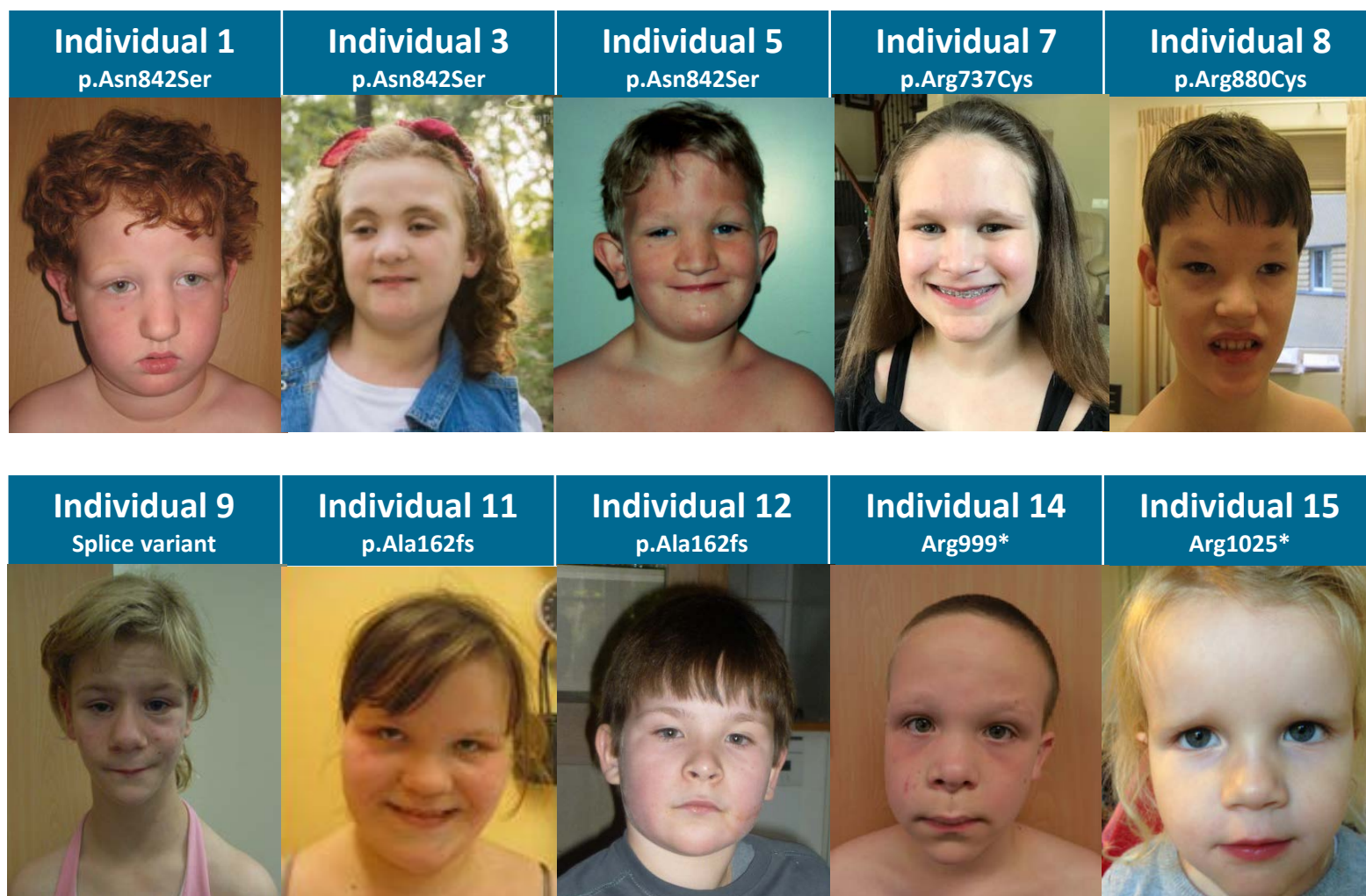


Table 1. Summary of major clinical features of individuals with variants in *CDK13*<sup>†</sup>

Individual	1	2	3	4	5	6	7	8	9 <sup>‡</sup>	10 <sup>‡</sup>	11	12	13	14	15	Cumulative
Gender	M	F	F	F	M	F	F	M	F	F	F	M	M	M	F	9 F, 6 M
Age at examination	6 y, 3 m	8 y	9 y	10 y, 1 m	22 y	11 y	13 y	9 y , 10 m	13 y	13 y	11 y	13 y	54 y	9 y	3 y, 4 m	
<i>CDK13</i> variant	c.2525A>G (p.Asn842Ser)	c.2525A>G (p.Asn842Ser)	c.2525A>G (p.Asn842Ser)	c.2525A>G (p.Asn842Ser)	c.2525A>G (p.Asn842Ser)	c.2141G>A (p.Gly714Asp)	c.2209C>T (p.Arg737Cys)	c.2638C>T (p.Arg880Cys)	c.2601-2A>G (splice site)	c.2601-2A>G (splice site)	c.484dup (p.Ala162fs)	c.484dup (p.Ala162fs)	c.484dup (p.Ala162fs)	c.2995C>T (p.Arg999*)	c.3073C>T (p.Arg1025*)	
Neurological and behaviour																
ID/DD	+ (moderate ID)	+ (moderate ID)	- (borderline ID)	+ (mild ID)	+ (moderate ID)	+ (moderate ID)	+ (DD/ID)	+ (borderline ID)	+ (mild ID)	+ (mild ID)	+ (mild ID)	+ (moderate ID)	+ (mild ID)	+ (borderline ID)	+ (DD)□	15/15
Feeding problems	+	+	+	-	+	-	+	+	-	+	+	+	+ (as child)	-	-	10/15
Head circumference (SD)	+1 SD	-1 SD	+ 1 SD	+ 0.75 SD	+0.39 SD	> 2.5 SD	+ 1 SD	0 SD	< -2.5 SD	< -2.5 SD	> 2.5 SD	+ 0.7 SD	+0.5 SD	+ 3 SD	+1.53 SD	3/15 macrocephaly; 2/15 microcephaly
Behavioural problems	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	15/15
Hypotonia	+	+	+	+	+	NR	+	+	+	+	-	+	NR	-	NR	10/12
Speech problems	+	+	+	-	+	+	NR	NR	NR	NR	NR	+	NR	NR	+	7/8
Sleeping problems	-	-	+	-	+ (until 12 y)	NR	-	+	-	-	NR	+	-	+	-	5/13
Congenital malformations																
Congenital heart defects	-	-	-	-	-	+	-	-	+	NR	-	-	NR	-	-	2/13
Structural brain abnormalities	NR	-	+	NR	+	NR	-	+	NR	NR	NR	-	NR	NR	-	3/7
Facial																
Flat midface	+	-	-	+	+	-	-	+	-	-	+	-	+	-	-	6/15
Blepharophimosis	+	-	-	-	+	+	-	+	-	+	-	+	+	-	-	7/15
Hypertelorism	+	-	-	-	+	+	-	+	-	-	+	-	+	-	-	6/15
Eye anomalies (strabismus)	-	+	+	+	+	-	+	+	-	+	+	-	+	+	-	10/15
Ear abnormalities	+	+	+	+	+	-	-	-	-	-	-	-	+	+	-	7/15
Broad nose/nasal bridge	+	+	+	+	+	-	-	-	+	+	+	+	+	-	+	11/15
Philtrum abnormalities	+	-	+	-	+	-	-	-	+	+	+	-	+	+	+	9/15
Thin lips (narrow mouth)	-	-	+	+	-	-	-	-	+	+	-	+	-	+	+	7/15
Small mouth	+	-	+	+	-	+	-	-	-	-	-	-	-	-	-	4/15
Others																
Sloping shoulders	+	-	+	+	+	NR	-	+	+	+	-	-	-	-	-	6/14
Gynaecomastia (males)	-	NA	NA	NA	+	NA	NA	+	NA	NA	NA	-	-	+	NA	3/5
Joint pathology	+	-	+	+	+	NR	+	NR	+	-	NR	-	NR	NR	-	6/10
Pes planus	-	-	+	-	+	NR	+	+	+	+	-	+	NR	+	+	9/13

Abbreviations are as follows: F, female; M, male; y, year; m, month; +, present; -, absent; NR, not reported; NA, not applicable

<sup>†</sup>Extensive clinical data are given in Suppl Table 1

<sup>‡</sup>Monozygotic twins

**Table 2. Overview of main clinical features of individuals with variants in *CDK13*<sup>†</sup>**

Study	Sifrim <i>et al.</i> , 2016	DDD Study, 2017	Bostwick <i>et al.</i> , 2017	Hamilton <i>et al.</i> , 2017	Current study	Cumulative
Number of described individuals	7	13	16	16	15	
Number of novel individuals <sup>‡</sup>	5 F, 2 M	6 F	4 F, 5 M	3 F	9 F, 6 M	27 F, 13 M
<b>Neurological and behaviour</b>						
ID/DD	7/7	6/6	9/9	3/3	15/15	40/40 (100%)
Feeding problems	7/7	5/6	NR	3/3	10/15	18/31 (58%)
Microcephaly	4/7	1/6	1/8	1/3	2/15	9/25 (36%)
Macrocephaly	0/7	0/7	0/8	0/7	3/15	3/25 (12%)
Behavioural problems	3/3	4/4	NR	1/1	15/15	23/23 (100%)
Hypotonia	3/7	2/4	9/9	1/2	10/12	25/34 (75%)
Speech problems	7/7	NR	9/9	NR	7/8	23/24 (96%)
Sleeping problems	2/2	1/1	NR	NR	5/13	8/16 (50%)
<b>Congenital malformations</b>						
Congenital heart defects	7/7	0/6	6/9	1/3	2/13	16/38 (42%)
Structural brain abnormalities	4/6	1/5	5/6	1/1	3/7	19/25 (76%)
<b>Facial</b>						
Flat midface	NR	1/1	NR	NR	6/15	7/16 (44%)
Blepharophimosis	2/5	6/6	NR	1/3	7/15	16/29 (55%)
Hypertelorism	4/7	2/6	6/8	1/3	6/15	19/39 (49%)
Eye anomalies	4/7	4/6	6/9	1/3	10/15	25/40 (63%)
Ear abnormalities	4/7	5/6	8/9	2/3	7/15	27/40 (68%)
Broad nose/nasal bridge	5/7	4/6	6/8	2/3	11/15	28/39 (72%)
Philtrum abnormalities	3/7	3/6	NR	0/3	9/15	15/31 (48%)
Thin lips (narrow mouth)	6/7	4/6	5/8	2/3	7/15	24/39 (62%)
<b>Others</b>						
Sloping shoulders	NR	NR	NR	NR	6/14	6/14 (43%)
Gynaecomastia (males)	NR	NR	NR	NR	3/5	3/5 (60%)
Joint pathology	1/7	1/6	NR	1/3	6/10	9/26 (35%)
Pes planus	NR	NR	NR	1/3	9/13	10/16 (63%)

Abbreviations are as follows: F, female; M, male; ; NR, not reported

<sup>†</sup>An overview of all reported individuals is given in Suppl Table 3.

<sup>‡</sup>Since some individuals have been reported multiple times over different reports, only the firstly published study is indicated here.  
Clinical information from later published studies on certain individuals is included in this overview.